Treatment of Chronic Myeloid Leukemia Following Imatinib Resistance:
A Nursing Guide to Second-Line Treatment Options

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The introduction of the BCR-ABL inhibitor imatinib revolutionized the treatment of patients with chronic myeloid leukemia (CML). However, resistance to imatinib has become a clinically significant issue, limiting its long-term efficacy. Numerous mechanisms have been associated with imatinib resistance, including mutations to the *BCR-ABL* gene, increased production of BCR-ABL, and activation of BCR-ABL–independent pathways (e.g., SRC-family kinases [SFKs]). Resistance to imatinib has driven the development of second-line therapies, such as dasatinib, a dual BCR-ABL/SFK inhibitor more potent than imatinib at targeting BCR-ABL. Dasatinib is approved for the treatment of patients with imatinib-resistant and -intolerant CML and Philadelphia chromosome–positive acute lymphoblastic leukemia. Nilotinib, an analog of imatinib, more potent than its parent compound, is another approved agent for patients with imatinib-resistant or -intolerant CML in the chronic or accelerated phase. Nurses must be aware of what constitutes a requirement for treatment change and the mechanisms of resistance that inform the choice of second-line agents. Oncology nurses also must ensure that patients have been educated appropriately to understand imatinib resistance and second-line treatment options. This article explores the mechanisms and identification of resistance and treatment options for when resistance occurs, as well as nursing implications.

Chronic myeloid leukemia (CML) is a clonal, myeloproliferative disorder of hematologic stem cells and accounts for 15% of adult leukemias in the United States (Jemal et al., 2007). CML progression usually occurs in three phases, including a chronic phase (CP) that most often is asymptomatic, an accelerated phase (AP), and a terminal blast phase (BP) (Sawyers, 1999). If CML is left untreated, progression from CP to BP usually occurs in three to five years (Sawyers). CML is characterized by a genetic translocation between chromosomes 9 and 22 (the Philadelphia chromosome). The translocation results in an abnormal fusion gene that encodes for the constitutively active BCR-ABL tyrosine kinase, the known causative agent underlying CML pathogenesis (Daley, Van Etten, & Baltimore, 1990; Faderl et al., 1999). The identification of this protein has made it an ideal target for therapeutic intervention.

The tyrosine kinase inhibitor (TKI) imatinib was the first BCR-ABL–targeted agent approved in 2001 for the treatment of patients with CML and has revolutionized the treatment of the disease. Unfortunately, resistance to imatinib has become a clinically significant problem that limits the long-term benefits of the drug in many patients with CML (Oestreicher, 2007a). The mechanisms that underlie imatinib resistance are multifactorial and should be considered carefully when healthcare professionals are choosing second-line treatment. This article discusses the

At a Glance

- Resistance to imatinib has become a significant clinical problem and has led to the development of second-line therapies, such as dasatinib and nilotinib.
- Nurses must be aware of what constitutes a requirement for treatment change and the mechanisms of resistance that inform the choice of second-line agents.
- Oncology nurses must ensure that patients are educated appropriately to understand imatinib resistance and available second-line treatment options.

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different mechanisms of imatinib resistance and the available treatment options for patients after imatinib failure.

Identifying Imatinib Resistance

Resistance to imatinib in CML is defined as either primary (intrinsic) or secondary (acquired). Primary imatinib resistance indicates a lack of efficacy at the onset of treatment (Hochhaus & La Rosée, 2004) and is identified based on failure to achieve time-based landmark responses, which have been outlined by the National Comprehensive Cancer Network (NCCN). Specifically, imatinib treatment is considered to have failed when any of the following has not been achieved: a complete hematologic response (CHR) by three months, any sign of a cytogenetic response by six months, a partial cytogenetic response (PCyR) by 12 months, or a complete cytogenetic response (CCyR) after 18 months of therapy (see Table 1 for response definitions). Patients who do not achieve these time-based milestones should be switched to alternate therapies (NCCN, 2008).

Primary imatinib resistance is perceived to be rare in patients with newly diagnosed CP CML; however, in reality, it does occur. In the pivotal phase III International Randomized Study of Interferon Versus STI571 (IRIS) trial of imatinib (400 mg per day) in newly diagnosed patients with CP CML, approximately 5% did not achieve a CHR with imatinib, 16% did not achieve a PCyR by 12 months, and 24% failed to achieve a CCyR by 18 months (Druker et al., 2006; O'Brien et al., 2003). Therefore, an estimated one-quarter of newly diagnosed patients had primary resistance to first-line imatinib (Hughes & Branford, 2006).

Acquired resistance develops after an initial response to imatinib therapy and is defined as a loss of a previously achieved response (hematologic or cytogenetic) or disease progression during imatinib treatment. Hematologic or cytogenetic relapse also should prompt an immediate change in treatment (NCCN, 2008). Acquired resistance often is associated with the emergence of BCR-ABL mutations that prevent imatinib from binding to its target (as discussed later) (Nardi, Azam, & Daley, 2004). Detection of such a mutation during first-line imatinib treatment constitutes a diagnosis of progression and should prompt a change in therapy. Acquired resistance was observed in a sizable number of patients treated in the phase III IRIS trial. Among those who initially responded to imatinib therapy, 17% subsequently relapsed and 7% progressed to advanced (AP or BP) CML after five years of treatment (Druker et al., 2006). In addition, the incidence of primary and acquired resistance increases as CML progresses (Lahaye et al., 2005). Response rates are lower among patients with advanced disease versus those in the CP, and most patients with advanced disease who initially respond eventually relapse (Druker et al.; Sawyers et al., 2002; Talpaz et al., 2002). The data highlight the importance of continuous monitoring of patients during imatinib treatment to detect secondary resistance as early as possible (Druker et al.).

Mechanisms of Imatinib Resistance

Although the mechanisms underlying primary imatinib resistance currently are unclear (Deininger & Holyoake, 2005), numerous mechanisms have been implicated in acquired resistance.

Table 1. Definitions of Response

RESPONSE	DEFINITION
Complete hematologic	White blood cells less than 1 × 10^9/L with normal differential Platelets less than 450 × 10^9/L
Cytogenetic	
Minor	35%–95% Philadelphia chromosome–positive (Ph+) metaphases
Major	Partial: 1%–35% Ph+ metaphases Complete: 0% Ph+ metaphases
Molecular[a]	
Major	More than three-log reduction from baseline or BCR-ABL/ABL ratio less than 0.1%
Complete	BCR-ABL/ABL ratio less than 0.001% or not detectable BCR-ABL transcripts by nested real-time polymerase chain reaction

[a] Molecular response is based on the level of BCR-ABL transcripts as measured by quantitative polymerase chain reaction.

Note. Based on information from Bocchia et al., 2006.

Such mechanisms include mutations of BCR-ABL, overexpression and amplification of BCR-ABL, increased activity of drug transporter proteins (Apperley, 2007; Frame, 2007), and activation of BCR-ABL–independent signaling pathways (specifically SRC-family kinases [SFKs], a family of eight molecules with a related structure). The most frequent and most well-studied mechanism of imatinib resistance is the occurrence of mutations in the BCR-ABL gene that prevent imatinib from binding, which thereby enables reactivation of BCR-ABL. More than 40 mutations within the BCR-ABL kinase domain have been identified to date (Hughes et al., 2006) and have been reported in patients with acquired resistance at a frequency of 40%–90% (Hochhaus, Kantarjian, et al., 2007; Hochhaus & La Rosée, 2004; Shah et al., 2002). The various mutations occur at different frequencies and confer different levels of imatinib resistance. Mutations that occur within the ATP-binding loop (P-loop) of the ABL kinase domain are the most frequently occurring during imatinib treatment, representing 30%–40% of identified mutations (Branford et al., 2003). Additionally, those mutations confer the highest level of resistance to imatinib, and studies have shown that patients harboring P-loop mutations have particularly poor outcomes (Branford et al.; Soverini et al., 2005). T315I is the second most frequently occurring mutation, which is completely resistant not only to imatinib (La Rosée, Corbin, Stoffregen, Deininger, & Druker, 2002) but also to all of the clinically available BCR-ABL inhibitors. Other imatinib-resistant mutations confer lower levels of resistance and, therefore, are considered to be of lesser clinical importance (Branford et al.; Hochhaus et al., 2002; Soverini et al.).

Resistance also can be caused by increased production of BCR-ABL, which results in a greater concentration for imatinib to inhibit. Additionally, alterations in the expression or activity of transporter proteins that affect intracellular drug concentrations can prevent imatinib from inhibiting BCR-ABL. In vitro studies have provided evidence that increased expression of multidrug resistance P-glycoprotein (Pgp) may contribute to imatinib resistance (Illmer et al., 2004; Mahon et al., 2000;

Thomas, Wang, Clark, & Pirmohamed, 2004). Pgp mediates resistance to an array of anticancer drugs by increasing their cellular effluxes (Ling, 1997). Imatinib is one such drug that can be removed from the cell through Pgp, and this protein has been implicated in imatinib resistance (Illmer et al.). Furthermore, reduced activity of organic cation transporter type 1 (OCT-1) has been shown to decrease the sensitivity of leukemia cells to imatinib in vitro (White et al., 2006). This protein mediates cellular uptake of imatinib, and decreased activity of OCT-1 reduces the uptake of imatinib by CML cells.

BCR-ABL–independent mechanisms also have been implicated in imatinib resistance. The SFKs are essential mediators of BCR-ABL signaling and are involved in CML disease progression (Danhauser-Riedl, Warmuth, Druker, Emmerich, & Hallek, 1996; Lionberger, Wilson, & Smithgall, 2000; Roginskaya et al., 1999). These signaling molecules can become independent of BCR-ABL, resulting in imatinib resistance (Ban et al., 2008; Dai, Rahmani, Corey, Dent, & Grant, 2004; Donato et al., 2003; Hu et al., 2006). Studies have shown that blocking BCR-ABL and SFKs simultaneously can overcome this form of resistance (Ban et al.; Dai et al.; Donato et al., 2003; Hu et al., 2006), suggesting that dual inhibition of SFKs and BCR-ABL would be clinically beneficial for patients who develop such resistance. For information about testing for these mutations, see Radich (2008).

Tyrosine Kinase Inhibitor–Based Treatment Options Following Imatinib Failure

Several treatment options are available for patients who experience progression on first-line imatinib. Hematopoietic stem cell transplantation (SCT) is still a valid treatment option for patients who have a suitable match-related or -unrelated donor. SCT offers potentially curative treatment but is associated with early morbidity and mortality. Three TKI-based treatment options are recommended for patients who are no longer responsive to first-line imatinib (NCCN, 2008). Escalating the dose of imatinib (to 600–800 mg per day) is one option for patients who experience treatment failure on standard doses (400 mg per day). Additionally, dasatinib and nilotinib are now approved by the U.S. Food and Drug Administration as second-line TKI treatments for patients following failure of first-line imatinib.

High-Dose Imatinib

Studies have shown that escalating the dose of imatinib to 600–800 mg per day can produce responses in certain refractory patient populations; however, most patients do not achieve sustained objective responses. Furthermore, dose escalation does not appear to benefit patients who have not achieved a prior cytogenetic response with standard-dose imatinib (Gambacorti et al., 2007; Kantarjian et al., 2004) and is not recommended for patients who develop BCR-ABL mutations (NCCN, 2008) (see Table 2). Additionally, high-dose imatinib is associated with increased toxicity, and many patients may not tolerate doses higher than 400 mg per day (Gambacorti et al.; Kantarjian et al., 2004).

Dasatinib

Dasatinib is a potent, orally administered dual BCR-ABL/SFK inhibitor approved in 2006 for the treatment of patients with imatinib-resistant or -intolerant CML or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL). This agent has a 325-fold greater potency against BCR-ABL in vitro (O'Hare et al., 2005) and inhibits almost all imatinib-resistant BCR-ABL mutants, except T315I (Shah et al., 2004; Tokarski et al., 2006). Importantly, dasatinib appears to maintain a high level of potency against the highly imatinib-resistant P-loop mutations (O'Hare et al.). However, dasatinib has diminished activity against less commonly occurring BCR-ABL mutants, such as F317L.

In addition, given the association of SFKs with imatinib resistance and leukemic progression, the anti-SFK activity of dasatinib also may provide a substantial treatment advantage for patients with imatinib-resistant disease (Donato et al., 2003, 2004, 2005; Hu et al., 2004, 2006; Wu et al., 2008). The activity of dasatinib also does not appear to be affected by Pgp or OCT-1 alterations (Hiwase et al., 2007; Kamath, Wang, Lee, & Marathe, 2008), indicating that dasatinib treatment can overcome resistance mediated by those transporter proteins.

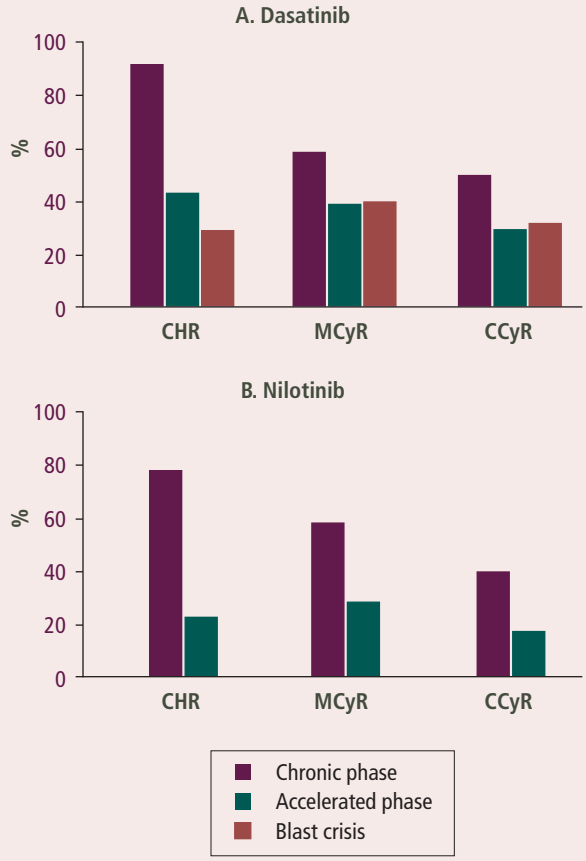
Dasatinib (70 mg orally twice daily) showed impressive efficacy in a series of open-label, phase II clinical trials of imatinib-resistant or -intolerant patients with all phases of CML and Ph+ ALL (Cortes et al., 2007; Guilhot et al., 2007; Hochhaus, Kantarjian, et al., 2007; Kantarjian, Pasquini, et al., 2007; Ottmann et al., 2007) (see Figure 1). Furthermore, the rate of response among patients with CP CML was similar among those with unmutated and mutant BCR-ABL, including patients harboring

Table 2. Second-Line TKIs Override Multiple Mechanisms of Resistance

	POTENTIAL TO OVERRIDE DIFFERENT MECHANISMS OF RESISTANCE		
RESISTANCE MECHANISM	HIGH-DOSE IMATINIB	DASATINIB	NILOTINIB
BCR-ABL overexpression	Yes	Yes	Yes
BCR-ABL mutation	No (most mutations remain resistant)	Yes (activity reduced against F317L [see Table 3]; ineffective against T315I)	Yes (activity reduced against certain P-loop mutations [see Table 3]; ineffective against T315I)
BCR-ABL–independent pathway	No	Yes; active against SFK-mediated resistance	Yes; inhibits LCK
Drug transporter protein (i.e., Pgp and OCT-1)	No	Yes	Yes

LCK—leukocyte-specific protein tyrosine kinase; OCT-1—organic cation transporter type 1; Pgp—P-glycoprotein; SFK—SRC-family kinase; P-loop—ATP binding loop; TKI—tyrosine kinase inhibitor

Note. Based on information from Kujawski & Talpaz, 2007; Lee et al., 2008.



CCyR—complete cytogenetic response; CHR—complete hematologic response; MCyR—major cytogenetic response

Figure 1. Summary of Responses in Phase II Trials

Note. Based on information from Baccarani et al., 2006; Cortes et al., 2007; Larson et al., 2007; Martinelli et al., 2006; Rosti et al., 2007.

P-loop mutations (Mueller et al., 2007). However, somewhat reduced activity was observed among patients with F317L mutations (Mueller et al.) (see Table 3).

In the only prospective comparison between two second-line treatments in CML, dasatinib showed superior efficacy compared with high-dose imatinib (800 mg per day) in a randomized phase II study (Src/Abl Tyrosine Kinase Inhibition Activity: Research Trials of Dasatinib [START]-R) of patients with CP CML who were resistant to first-line imatinib (400–600 mg per day). With a median follow-up of 15 months, the major cytogenetic response rate was improved with dasatinib compared with high-dose imatinib (52% versus 33%, p = 0.02), and CCyRs were achieved in a significantly larger number of patients receiving dasatinib (40% versus 16%, p = 0.004).

In the phase II trial, dasatinib generally was well tolerated, and nonhematologic adverse events were mostly mild to moderate in severity (Galinsky & Buchanan, 2009). Grade 3 or 4 neutropenia and thrombocytopenia were common in patients with CP CML (46% and 41%, respectively) and grade 3 or 4 anemia occurred in 18% (Bristol-Myers Squibb Company, 2009). However, cytopenic events usually were reversible and could be managed effectively by dose interruption or reduction (Galinsky & Buchanan). Of note, in patients with advanced disease, cytopenias may reflect the activity of dasatinib against leukemic cells. Nonhematologic toxicity consisted mainly of mild to moderate gastrointestinal symptoms (nausea and vomiting), pleural effusions, and other fluid-retention events. Pleural effusions often can be managed with dose modification and, when necessary, diuretic or steroid therapy (Galinsky & Buchanan). However, severe events may require oxygen therapy or thoracentesis (Bristol-Myers Squibb Company). See Table 4 for adverse events and monitoring requirements. Although dasatinib rarely causes prolongation of cardiac ventricular repolarization (QT interval), it should be administered with caution in patients who have or are at risk for this event, including those with hypokalemia, hypomagnesemia, or congenital long QT syndrome, or those receiving concomitant medication that may have that effect. Hypokalemia and hypomagnesemia should be corrected before dasatinib administration (Bristol-Myers Squibb Company). Importantly, cross-intolerance does not seem to occur with dasatinib and imatinib (Cortes et al., 2007; Guilhot et al., 2007; Hochhaus, Kantarjian, et al., 2007; Kantarjian, Pasquini, et al., 2007; Ottmann et al., 2007).

Recent data from a phase III study of patients with imatinib-resistant or -intolerant CP CML have shown that a dosage of 100 mg once daily offers a more favorable risk/benefit profile compared with the previously recommended starting dose of 70 mg twice daily (Bryant, 2009; Shah et al., 2008). The 100 mg once-daily dose demonstrated equivalent efficacy compared with 70 mg twice daily and was associated with a significantly lower incidence of all grades of pleural effusion (7% versus 16%, p = 0.03) and grade 3 or 4 thrombocytopenia (22% versus 37%, p = 0.004). Furthermore, fewer discontinuations and dose modifications occurred in the 100 mg once daily arm versus the 70 mg twice daily arm. Based of the results of the trial, the recommended starting dose of dasatinib for imatinib-resistant or -intolerant patients with CP CML recently was changed to 100 mg once daily (Bristol-Myers Squibb Company, 2009). The recommended starting dose for patients with advanced disease (AP or BP CML or Ph+ ALL) is 140 mg administered once daily. See Table 5 for administration instructions, contraindications, and drug interactions. Dasatinib may be taken with or without a meal.

Nilotinib

Nilotinib is an efficacious, orally administered analog of imatinib approved for the treatment of patients with CP or AP CML resistant to or intolerant of prior imatinib treatment (Novartis Pharmaceuticals Corporation, 2007). This agent has 20- to 50-fold greater in vitro activity against BCR-ABL compared with imatinib and is effective against most BCR-ABL mutants. However, preclinical data show that it has a diminished effect against certain mutations, such as those within the P-loop and F359V (O'Hare et al., 2005; Weisberg et al., 2005). Until recently, nilotinib was not thought to be active against most SFKs, but it has been found to inhibit the SFK leukocyte-specific protein tyrosine kinase, and therefore may have activity in patients with SFK-mediated resistance (Blake, Lyons, & Hughes, 2008; Jabbour, Cortes, Giles, O'Brien, & Kantarjian, 2006; Manley, Bruggen, Fabbro, Martiny-Baron, & Meyer, 2007; O'Hare et al.).

Nilotinib (400 mg twice daily) was approved in 2007 based on results from a single phase II open-label trial in patients with

Table 3. Efficacy of Dasatinib and Nilotinib in Patients With Chronic-Phase Chronic Myeloid Leukemia Harboring Specific Mutations

	DASATINIB		NILOTINIB	
TYPE OF MUTATION	ACTIVITY	CCyR (%)	ACTIVITY	CCyR (%)
Any mutation	++	40 (158/369)	++	32 (32/99)
Y253F/H (P-loop)	++	52 (12/23)	–	0 (0/8)
E255K/V (P-loop)	++	33 (8/24)	–	0 (0/8)
F317L (P-loop)	+	7 (1/14)	++	NR[a]
F359C/V	++	52 (14/27)	–	0 (0/10)

[a] Considered a nilotinib-sensitive mutation (40% [18 of 45] of patients harboring such nilotinib-sensitive mutations achieved CCyR) (Hughes et al., 2007)

CCyR—complete cytogenetic response; NR—not reported; P-loop—ATP binding loop

Note. Nilotinib data are based on 275 patients with chronic-phase chronic myeloid leukemia (CP CML) enrolled in clinical trials and who had mutational data available (Hughes et al., 2007). Dasatinib data are based on 1,094 patients with CP CML enrolled in clinical trials with dasatinib (Hochhaus, Branford, et al., 2007).

Note. Based on information from Hochhaus, Branford, et al., 2007; Hughes et al., 2007.

CP or AP CML following imatinib failure. Marked activity was observed in patients with CP or AP CML resistant to or intolerant of imatinib (Kantarjian, Hochhaus, et al., 2007; le Coutre et al., 2007). After 18 months of follow-up in patients with CP CML, MCyRs were achieved in 57% of patients (with a median time to response of 2.8 months), and CCyRs in 41% (Kantarjian et al., 2008). Substantial efficacy was observed in patients with most imatinib-resistant BCR-ABL mutations. Consistent with preclinical findings, response rates were reduced among patients with certain P-loop mutations (E255K/V and Y253H) and those with F359C/V mutations (Hughes et al., 2007).

Nilotinib was generally well tolerated in clinical trials. In patients with CP CML, 28% of patients experienced grade 3 or 4 thrombocytopenia, and 30% experienced grade 3 or 4 neutropenia; grade 3 or 4 elevations in biochemical parameters related to liver and pancreatic functions were observed in less than 15% of patients (Kantarjian et al., 2008). The events usually were manageable and reversible with dose interruption or reduction.

Prolongation of the QTc interval and sudden deaths occurred in clinical trials, believed to be related to ventricular repolarization abnormalities resulting from nilotinib therapy. Increase in QTcF more than 60 msec from baseline was observed in 2.1% of the patients and QTcF of more than 500 msec was observed in three patients (less than 1%). Incidence of sudden death was 0.6% in a large clinical study and confirmed at this rate in an expanded access program. This resulted in a black-box warning being added to the prescribing information. Because plasma levels of nilotinib are increased with food, patients should not eat for at least two hours before and one hour after administration. Any electrolyte imbalance should be corrected before nilotinib therapy and monitored thereafter (Novartis Pharmaceuticals Corporation, 2007). Little cross-intolerance exists between imatinib and nilotinib, other than thrombocytopenia (Jabbour et al., 2008).

Monitoring Patients for Imatinib Failure

Before the availability of dasatinib and nilotinib, patients with imatinib-resistant CML had a poor prognosis (Ault, 2007). Second-line TKIs provide new hope for patients who experience failure of front-line imatinib (including those with imatinib resistance or intolerance). However, as with most treatment methods for CML, the second-line agents are most effective when administered in the CP rather than in advanced disease (Cortes et al., 2007; Guilhot et al., 2007; Hochhaus, Kantarjian, et al., 2007; Kantarjian, O'Brien, et al., 2007). Therefore, healthcare professionals must monitor patients during treatment with imatinib to identify imatinib resistance as early as possible and to ensure that they receive the most effective therapy before disease progression.

The NCCN (2008) has outlined recommendations for monitoring response to imatinib treatment in CML. Cytogenetic testing is recommended at 6 months and 12 months after the start of therapy (refer to Zeidan, Wang, & Wetzler, 2008). If a CCyR is not achieved by 12 months, another cytogenetic evaluation should be conducted at 18 months. Treatment should be altered in patients who do not achieve any of the following: a CHR by three months, any sign of a cytogenetic response by six months, a PCyR by 12 months, or CCyR by 18 months of therapy (Zeidan et al.).

Once a CCyR has been reached, cytogenetic testing no longer can be used to monitor response because, by definition, all of the Ph+ metaphases have been eliminated. However, measurement of BCR-ABL transcript levels by quantitative polymerase chain reaction (PCR) is useful for continued response monitoring following the achievement of CCyR. The NCCN (2008) recommends that when a patient appears to be responding to therapy (particularly once a CCyR is achieved), BCR-ABL transcript levels in the peripheral blood be measured every three months.

Rising levels of BCR-ABL may be associated with an increased risk of imatinib-resistant mutations. Therefore, a one-log rise in BCR-ABL—confirmed by two measurements taken a maximum of one month apart—should prompt mutation analysis as well as cytogenetic evaluation and more frequent monitoring of BCR-ABL levels (i.e., once a month). Currently, no guidelines exist for changing therapy based on rising BCR-ABL transcripts alone.

As mentioned previously, detection of an imatinib-resistant mutation supports the diagnosis of imatinib resistance and helps to identify the second-line treatment most suitable for an individual patient. Therefore, screening for such mutations is an important component of response monitoring. For patients in the CP, screening for BCR-ABL mutations is recommended if an inadequate initial response occurs; screening also should be performed on patients with any indication of a loss of

Table 4. Adverse Events and Monitoring Requirements for Imatinib, Dasatinib, and Nilotinib

DRUG	COMMON AND SEVERE ADVERSE EVENTS	MONITORING REQUIREMENTS
High-dose imatinib	The following adverse events were reported for standard-dose (400 mg per day) imatinib. **Common (20% or more of patients)[a]:** cytopenias, fluid retention, nausea, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, headache, joint pain, abdominal pain, nasopharyngitis, hemorrhage, myalgia, vomiting, cough, and upper respiratory tract infection **Severe[a]:** neutropenia (17%), thrombocytopenia (9%), anemia (4%), musculoskeletal pain (5%), muscle cramps (2%), diarrhea (3%), rash and desquamation of the skin (3%), fluid retention (3%), liver toxicity (elevated bilirubin [1%], SGOT/SGPT [5%], and alkaline phosphatase [less than 1%]), hemorrhage (2%), and severe cardiac failure and left ventricular dysfunction (less than 1%) Compared with first-line, standard-dose imatinib, the risks of hematologic and nonhematologic toxicities significantly rise if high-dose imatinib is employed as a second-line agent.	Severe congestive heart failure and left ventricular dysfunction: Monitor for cardiac failure in patients with cardiac disease or risk factors for cardiac failure periodically throughout therapy. Hematologic toxicity: Monitor complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter. Hepatotoxicity: Monitor bilirubin, AST/ALT, and alkaline phosphatase at treatment initiation and then monthly, or as clinically indicated. Fluid retention and edema: Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. Unexpected rapid weight gain should be investigated carefully.
Dasatinib	**Common (20% or more of patients)[b]:** fluid retention, diarrhea, headache, skin rash, nausea, hemorrhage, fatigue, and dyspnea **Severe[b]:** neutropenia (59%), thrombocytopenia (57%), anemia (37%), pleural effusion (9%), pyrexia (3%), pneumonia (3%), infection (2%), febrile neutropenia (4%), gastrointestinal bleeding (4%), dyspnea (3%), sepsis (1%), diarrhea (2%), congestive heart failure (2%), and pericardial effusion (1%)	Hematologic toxicity: Monitor complete blood counts weekly for the first two months and monthly thereafter, or as clinically indicated. Fluid retention/pleural effusion: Perform chest x-ray if patients develop symptoms suggestive of pleural effusion (e.g., dyspnea, dry cough).
Nilotinib	**Common (20% or more of patients)[c]:** thrombocytopenia, neutropenia, rash, headache, nausea, pruritus, fatigue, diarrhea, and constipation **Severe[c]:** thrombocytopenia (30%), neutropenia (30%), anemia (12%), leukopenia (percentage not reported), febrile neutropenia (1%–10%), pneumonia (1% or less), intracranial hemorrhage (1% or less), pyrexia (1%), elevated serum lipase (16%), liver toxicity (elevated bilirubin [10%], AST/ALT [4%], and alkaline phosphatase [2%]), and QT prolongation (1%–10%). Five sudden deaths were reported in an ongoing clinical study (N = 867) and were attributed to ventricular repolarization abnormalities.	QT interval prolongation: electrocardiogram at baseline, seven days after initiation, periodically throughout therapy, and following dose adjustments Hematologic toxicity: Monitor complete blood counts every two weeks for the first two months and monthly thereafter. Electrolyte abnormalities: Monitor potassium, phosphate, calcium, and sodium periodically throughout therapy. Liver function abnormalities: Monitor bilirubin, AST/ALT, and alkaline phosphatase periodically throughout therapy. Elevated serum lipase: Monitor serum lipase periodically throughout therapy.

[a] Data from 551 patients with newly diagnosed chronic myeloid leukemia enrolled in the phase III International Randomized Study of Interferon Versus STI571 trial (starting dosage 400 mg per day)

[b] Pooled data from 2,182 patients with chronic-phase, accelerated-phase, or blast-phase chronic myeloid leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia in clinical studies (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily)

[c] Pooled data from 438 patients with chronic-phase or accelerated-phase chronic myeloid leukemia in clinical studies (starting dosage 400 mg twice daily)

AST/ALT—aspartate aminotransferase/alanine aminotransferase; SGOT/SGPT—serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase

Note. Based on information from Bristol-Myers Squibb Company, 2009; Novartis Pharmaceuticals Corporation, 2006, 2007.

response, including hematologic or cytogenetic relapse, or a rise in BCR-ABL transcript levels. Because BCR-ABL mutations frequently are present in patients with advanced disease, mutational screening should be performed routinely (every three months) in such patients, regardless of treatment response.

Guidelines for Second-Line Treatment

Upon detection of primary or acquired imatinib resistance, treatment should be changed promptly. The NCCN (2008) provided general guidelines for changing treatment following

Table 5. Administration Instructions, Contraindications, and Potential Drug Interactions for Imatinib, Dasatinib, and Nilotinib

VARIABLE	HIGH-DOSE IMATINIB	DASATINIB	NILOTINIB
Indication	All phases of CML	All phases of CML and Ph+ ALL	CP and AP CML
Dose and schedule	600 mg once daily or 400 mg twice daily	CP: 100 mg once daily Advanced phase: 140 mg once daily	400 mg twice daily
Administration instruction (fasting requirement)	Orally 800 mg total daily dose should be administered as 400 mg twice daily—once in the morning and once in evening. Doses should be taken with a meal and a large glass of water.	Orally, swallowed whole Once-daily dose (CP) can be administered in the morning or evening. Twice-daily dose (advanced phase) should be administered once in the morning and once in the evening. Doses can be taken with or without food.	Orally, swallowed whole with water Doses should be administered at approximately 12-hour intervals. No food should be consumed for at least two hours before and one hour after a dose is administered.
Contraindication	None	Use caution with patients with known lung problems (e.g., existing pleural effusion).	Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome.
Potential drug interaction	CYP3A4 inhibitors and inducers may affect serum concentration. Imatinib may alter the plasma concentration of drugs eliminated by CYP3A4. Imatinib may increase systemic exposure to substrates of CYP2D6. Patients who require anticoagulation should receive low-molecular-weight or standard heparin instead of warfarin. Imatinib may increase systemic exposure to acetaminophen.	CYP3A4 inhibitors and inducers may affect serum concentration. Dasatinib may alter the plasma concentration of drugs eliminated by CYP3A4. Antacids may decrease dasatinib levels. Proton pump inhibitors may decrease dasatinib levels.	CYP3A4 inhibitors and inducers may affect serum concentration. Nilotinib may increase the plasma concentration of drugs eliminated by CYP3A4, CYP2C6, CYP2C9, CYP2D6, or UGT1A1. Drugs that inhibit Pgp may increase nilotinib concentrations.

AP—accelerated phase; CML—chronic myeloid leukemia; CP—chronic phase; Pgp—P-glycoprotein; Ph+ ALL—Philadelphia chromosome–positive acute lymphoblastic leukemia

Note. Based on information from Bristol-Myers Squibb Company, 2009; Novartis Pharmaceuticals Corporation, 2006, 2007.

imatinib failure. Patients with primary imatinib resistance should be switched to dasatinib or nilotinib or evaluated for SCT or entry into a clinical trial. If tolerable, high-dose imatinib (600–800 mg per day) also may be considered for patients with a minor cytogenetic response or PCyR by six months or a PCyR by 12 or 18 months. For patients who experience a loss of a hematologic or cytogenetic response or who progress to advanced disease during imatinib treatment, dasatinib or nilotinib is recommended, followed by SCT, if feasible. Such patients also may be considered for participation in a clinical trial.

BCR-ABL mutations should be used as a guide to selecting second-line treatment following the development of imatinib resistance. In particular, because dasatinib and nilotinib have differential activity against specific mutations, the results from mutation screening may be used to choose between the two treatments. In this regard, dasatinib may be the most appropriate treatment for patients harboring an F359C/V or P-loop mutation, whereas nilotinib may be a better choice for patients harboring F317L mutations (Hughes et al., 2007). However, further studies are necessary before definitive guidelines can be established for TKI treatment decisions based on the presence of specific mutations. Nonetheless, neither dasatinib nor nilotinib is clinically effective against T315I mutations, and patients harboring such a mutation should be considered for SCT or a clinical trial (NCCN, 2008).

Implications for Nursing

Nurses can continue to help patients living with CML to confront difficult decisions during life-long therapy for their disease (Breed, 2003; D'Antonio, 2005; Shannon-Dorcy & Wolfe, 2003). As highlighted earlier in this article, second-line TKIs are most effective when administered before progression to advanced disease. Therefore, identifying imatinib resistance as early as possible is imperative to ensure the best chance for positive treatment outcomes. Best clinical practice may require an increase in monitoring to detect early signs of resistance, and nurses may be required to explain the need for more frequent tests (e.g., PCR, mutation analysis, complete blood counts, marrow biopsies) (Ault, 2007). Patients should be counseled on the early signs of adverse events commonly associated with their treatments, and they should be aware of the importance of identifying adverse events before they become serious. Additionally, patients should be encouraged to discuss any potential adverse events they

Table 6. Recommendations to Assist With the Management of Adverse Events

ADVERSE EVENT	RECOMMENDATION
Pleural effusion	
Grade 2	Discontinue therapy until symptoms resolve and then restart treatment at same dose. If symptoms recur, discontinue treatments until symptoms resolve and then reduce the dose of treatment. Diuretic or steroids may be used if needed.
Grade 3	Discontinue therapy, diuretics, or steroids until symptoms resolve. Pulmonary consultation may be indicated for thoracentesis or a pleuravac catheter.
Grade 4	Severity of this adverse event is life-threatening. Discontinue drug.
Peripheral edema or periorbital edema	Discontinue therapy until symptoms resolve and then restart treatment at same dose. If symptoms recur, discontinue treatments until symptoms resolve and then reduce the dose of treatment. Diuretic may be needed.
Nausea and vomiting	
Grade 1	Maintain current treatment regimen with the addition of an appetite stimulant, antiemetic, or change in dosing schedule (e.g., administer medication in the evening instead of morning).
Grade 2 or 3	Discontinue therapy and, if needed, administer IV fluids for dehydration. When symptoms resolve, challenge with the same treatment dose. If symptoms recur, reduce the treatment dose.
Grade 4	Discontinue drug.
Rash	
Grade 1	Discontinue therapy until symptoms resolve and then restart treatment at same dose. If symptoms recur, consider a dose reduction.
Grade 2 or 3	Discontinue therapy as above. Topical or systemic steroids and antihistamines may be used for symptom management, followed with a dose reduction of 25%.
Grade 4	Discontinue drug.
Fatigue	
Grade 1 or 2	Recommend activity rest and stress management, monitor the patient's sleep patterns, and evaluate nutritional status. Check other potential second disease processes (e.g., thyroid function, adrenal insufficiency, bleeding, electrolyte imbalances, psychosocial issues).
Grade 3	Discontinue therapy for a short duration. If symptoms resolve, restart treatment at a lower dose. If symptoms persist, consider pharmacologic interventions with psychostimulants, low-dose corticosteroids, or antidepressants before discontinuing therapy.
Grade 4	Discontinue drug.
Cytopenia[a]	
Grade 1 or 2; CP CML	Endure cytopenia until counts normalize.
Grade 3 or 4; CP CML	Discontinue therapy until counts normalize. Challenge with the same treatment dose, and if symptoms recur, discontinue treatment until counts normalize and continue treatment with a dose reduction of 25%.
AP/BP CML	Medication is used as a salvage therapy. Surpassing the initial cytopenia within six weeks is a critical treatment landmark (refer to Src/Abl Tyrosine Kinase Inhibition Activity: Research Trials of Dasatinib for blast phase chronic myeloid leukemia). Support patients with packed red blood cell and platelet transfusions for the first month if needed.

[a] Cytopenia grade 1 defined as hemoglobin less than 10 g/dl, absolute neutrophil count less than 1,500 cells/mcl, platelets less than 75,000/mcl; grade 2 defined as hemoglobin less than 10–8.0 g/dl, absolute neutrophil count less than 1,500–1,000 cells/mcl, platelets less than 75,000–50,000/mcl; grade 3 defined as hemoglobin less than 8.0–6.5 g/dl, absolute neutrophil count less than 1,000–500 cells/mcl, platelets less than 50,000–25,000/mcl; grade 4 defined as hemoglobin less than 6.5 g/dl, absolute neutrophil count less than 500 cells/mcl, platelets less than 25,000/mcl.

AP/BP CML—accelerated phase or blast phase chronic myeloid leukemia; CP CML—chronic-phase chronic myeloid leukemia

Note. Based on information from National Cancer Institute, 2006; Portenoy & Itri, 1999.

experience with their healthcare providers so that they may be managed appropriately (see Table 6).

As always, when a patient changes therapy, nurses must be cognizant of differences in doses and administration schedules as well as any potential drug interactions (Oestreicher, 2007a).

Accurate patient education should follow any change in therapy to ensure that patients follow the instructions and take their drugs as prescribed. Furthermore, potential drug interactions must be discussed clearly with patients so that all medications are taken into account, even over-the-counter medications and herbal supplements. Nurses should educate patients about administration instructions, contraindications, and potential drug interactions for imatinib, dasatinib, and nilotinib.

As with any treatment, adverse events associated with these second-line treatments should be taken into consideration, and nurses should be knowledgeable about the different safety profiles of imatinib, dasatinib, and nilotinib (Ault, 2007; Ault, Kaled, & Rios, 2003; Stull, 2003). Side effects usually are mild and manageable with supportive care measures (Ault; NCCN, 2008); however, severe adverse events may require dose modifications, additional interventions, or a change to a different TKI. Nurses must be familiar with the appropriate management of adverse events associated with different treatment options.

Compliance also is a critical issue with oral oncolytics, such as imatinib, dasatinib, and nilotinib. Patients may want to discontinue therapy if they have a good response or if they

experience discomforting adverse events. Nurses should ensure compliance to avoid risk of relapse should a patient stop medication (Oestreicher, 2007b). Educating patients on the risks of discontinuing therapy may improve their adherence to self-administered oral chemotherapy (Hartigan, 2003; Kaplow, 2005). Nilotinib has a fasting requirement for drug administration. Nurses should highlight to patients the importance of following such requirements. Studies with other medications have reported that many patients have difficulty adhering to fasting requirements and that hunger caused by such requirements is a primary cause of nonadherence (da Silveira, Drachler, Leite, & Pinheiro, 2003; Gallant & Block, 1998; Papaioannou, Kennedy, Dolovich, Lau, & Adachi, 2007). Choosing the most appropriate second-line treatment also should involve consideration of each patient's previous side-effect profile. Patients with a history of cardiac problems should not be prescribed nilotinib, whereas dasatinib should be avoided in patients with lung problems.

Conclusion

Resistance to imatinib has emerged as a significant clinical issue, and the underlying mechanisms are multifactorial. Fortunately, several second-line TKIs are available for the treatment of patients with resistance to first-line imatinib. The benefit of administering second-line therapy before progression to advanced disease highlights the importance of identifying patients with imatinib resistance as early in the disease course as possible. Nurses can play a major role in identifying such patients and should be conscious of the signs of resistance. Furthermore, the second-line TKIs are differentially effective against each mechanism of resistance; healthcare professionals should consider the differences when choosing the most appropriate treatment.

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